

Draw Pharmacology *in your mind*



General Pharmacology

If you are a pharmacy student
If you are postgraduate and want
to revise pharmacology by an
easy way
If you are using any pharmacology
reference
this file will aid you
> And wait for more <

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What is Pharmacology ?

It is the science that deals with the study of chemical substances (Drugs)

What they are ?

Sources, Chemical & Physical properties

How they work ?

Mechanism of actions , Side effects

What they do ?

Biological effects , Therapeutic use, Pharmacokinetics and Pharmacodynamics .. etc

GENERAL PHARMACOLOGY

Drugs: any chemical substance that can affect living tissues and can be **used in diagnosis , prevention or treatment** of diseases

Sources of Drugs

Natural

- Plant** ex. Digitalis Glycosides - atropine
- Animals** ex. Heparin - insulin
- Microorganisms** ex. Antibiotics (Penicillin)
- Minerals** ex. Ferrous Sulphate - Magnesium sulphate

Synthetic

ex. Sulphonamides

Semisynthetic

ex. Homatropine methyl bromide

Biosynthetic

Genetically engineered drugs

ex. Recombinant DNA Human Insulin

the gene responsible for insulin synthesis is incorporated into genome of E.coli

Pharmacokinetics

What the **BODY** does to the **DRUG**

ADME

- Absorption
- Distribution
- Metabolism
- Excretion

Pharmacodynamics

What the **DRUG** does to the **BODY**

Mechanism of action

Pharmacological effect = Clinical response

PHARMACODYNAMICS

How does the drug affect the body ?

Through its action on

Ion Channels

Carriers

Enzymes

Receptors

Proteinaceous macromolecules exist mainly on cell surface and part of them may exist intracellular. They receive the drug, hormones or transmitter substances that occur naturally in the body --> Series of changes within the cell occur --> **and then that gives response** such as muscle contraction or relaxation, controlling glands secretion ... etc

Any drug or substance binds to the receptor activating or inactivating it is called "**Ligand**"

What is ?

Types ?

Channel-linked receptors / Ligand-gated ion channels

G-Protein coupled receptors

Enzyme-linked (Tyrosin kinase-linked) receptors

Nuclear receptors

We need first to know "Membrane Potential"

We have 4 main types of ions that manage the electricity in our body : Na^+ , K^+ , Ca^{+2} , Cl^-

Na^+ , Ca^{+2} and Cl^- at the **outer side** the cell membrane and K^+ at the **inner side** the cell membrane

In **Normal** state (**Resting membrane potential**) the membrane is **Polarized** (+ve charge outside and -ve charge inside)

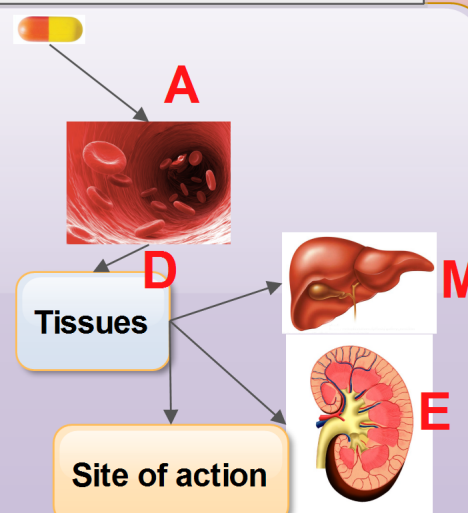
When Na^+ or Ca^{+2} enters in this case the membrane is **Depolarized** "excitation"

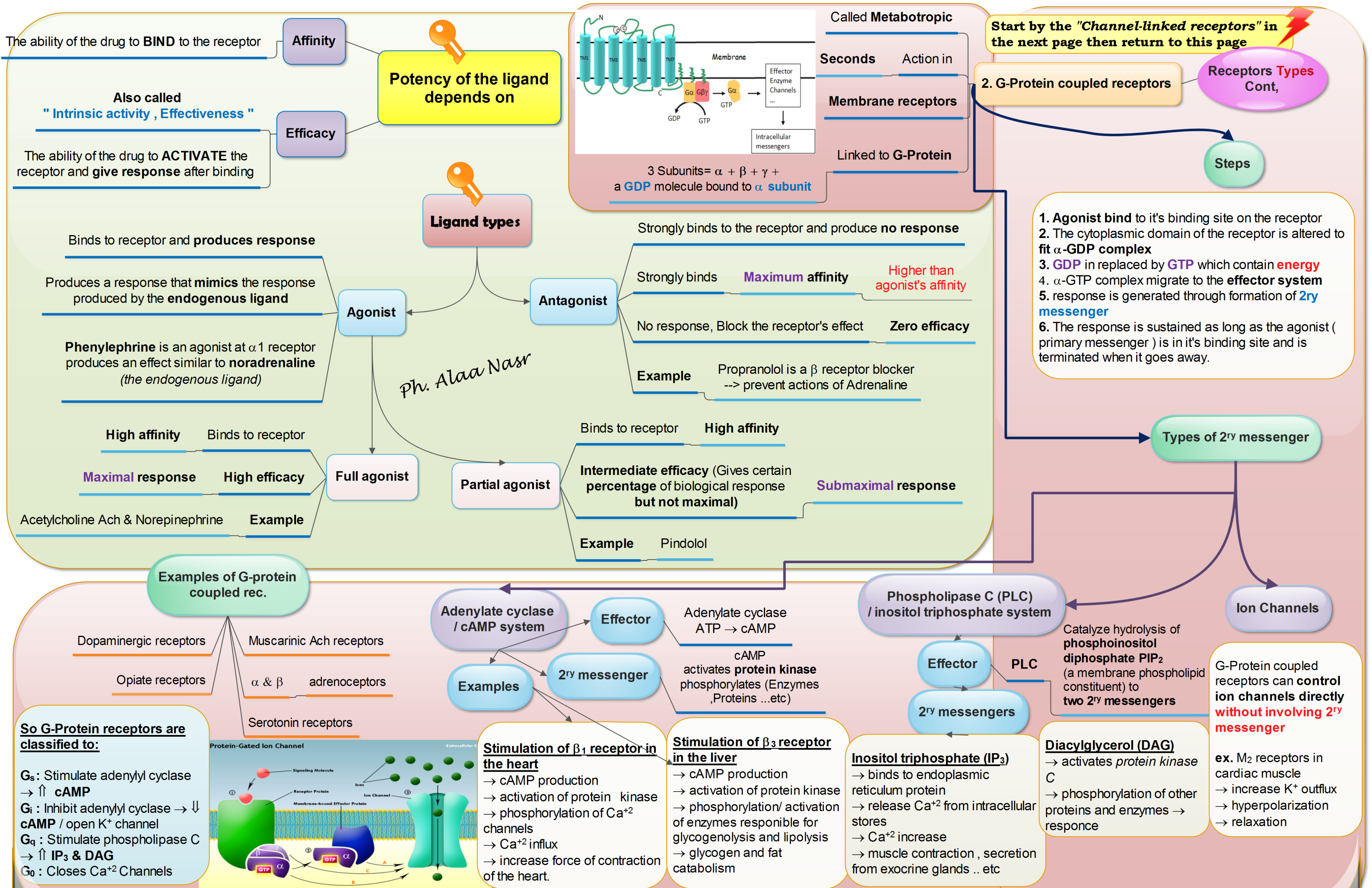
In case of K^+ **outflux** or Cl^- **influx** the membrane it makes outer side more +ve and inner side more -ve this is called "**Hyperpolarization**" "inhibition"

As illustrated in the figure (1)

Outer side	+	+	+	+	+
Inner side	-	-	-	-	-
	+	+	+	+	+
	-	-	-	-	-
	-	-	-	-	-
	+	+	+	+	+
Hyperpolarization					
Depolarization					

Figure (1)





Ph. Alaa Nasr

Receptors Types Cont,

3. Enzyme-linked (Tyrosin kinase-linked) receptors

Membrane receptors

Effector domain (Cytoplasmic domain)

Contain an **enzyme** as a part of their structures

Mostly **"Tyrosine kinase"**

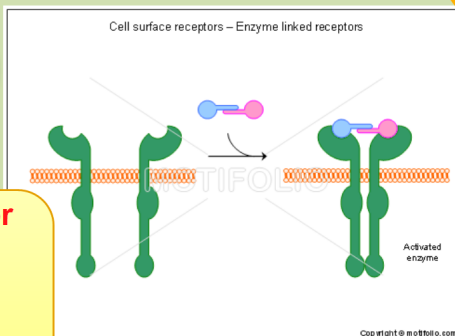
Other enzymes
Serine Kinase, Threonine Kinase and Guanylyl cyclase

Mechanism

→ When the agonist binds to the receptor
→ assembly of **two** receptors to form dimer
→ activates **tyrosine kinase**
→ Leading to **phosphorylation** of **tyrosine residue** in the receptor and on other specific signalling proteins
→ **final response**

Examples

1. **Insulin receptor**
2. **Epidermal growth factor receptors**
3. **Growth hormone receptors**



Examples for the carriers

- The carriers which are responsible for
1. Transporting **glucose** and **aminoacids** **into** cell
 2. Transporting **Na⁺** and **Ca²⁺** ions **out** of cell
 3. **Reuptake** of neurotransmitters

Examples of drugs targeting carriers

1. **Proton Pump Inhibitors "PPIs"** (ex. **Omeprazole**) which inhibit **H⁺/K⁺ ATPase pump** which is responsible for transporting of H⁺ against concentration gradient in stomach
2. **Tricyclic antidepressants "TCAs"** inhibit the **reuptake of noradrenaline**

1. Channel-linked receptors / Ligand-gated ion channels

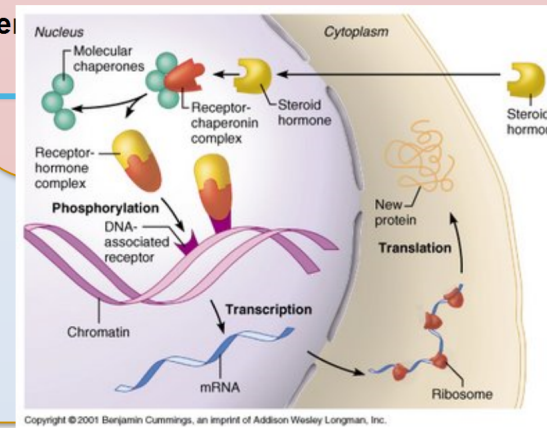
Called also **Ionotropic**

Membrane receptors

Linked to ion channels

So, they are responsible for opening the channel when activated
→ flow of ions → response

Synaptic transmission **Milliseconds**



4. Nuclear receptors

Intracellular receptors

Very slow in action

So, the agonist must enter the cell to reach the **Highly lipophilic**

Their action is obtained through **synthesis of new proteins or enzymes**

Examples

1. **Steroidal hormone receptors**
2. **Vitamin D receptors**
3. **Thyroid receptors**

Activation of nuclear receptors → transcription of DNA → mRNA → Protein synthesis → response

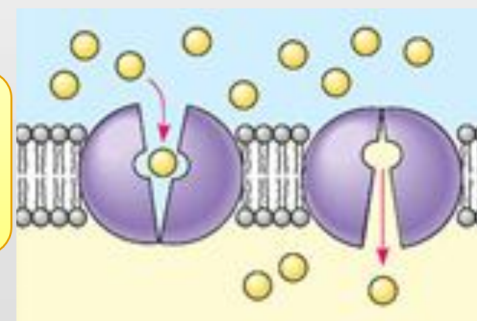
Now we have just finished talking about **"Receptors"** .. look back **"Carriers"**, **"Enzymes"**, **"Ion channels"** are left, So let's talk about

Carriers

What is ? **Proteins**

What they do ?

Polar molecules could not just pass through the phospholipid membrane, so they need **"carrier"** that helps them moving across the cell membrane (**Small organic molecules and ions**)



Enzymes

Enzymes can be the target of a certain drug, so the drug **inhibit the enzyme's activity**

Examples

1. Irreversible inhibition of **cyclooxygenase enzyme COX** enzymes by **Aspirin**
2. Reversible inhibition of **cholinesterase enzyme** by **neostigmine**

Ion Channels

2 types

They are **transmembrane pores** surrounded by **protein subunits**

Self-operated channels (Direct channels)

Serves as **direct target for the drug (Voltage gated Na⁺, Ca²⁺, K⁺, Cl⁻ channels)** → Change voltage across the cell membrane

Receptor-operated channels (linked to receptors)

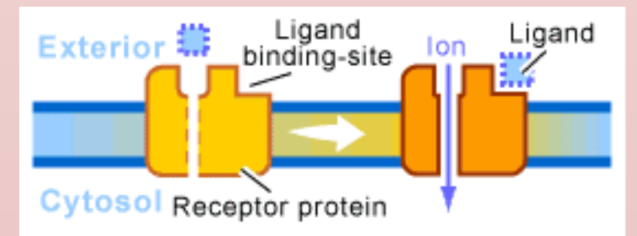
Examples

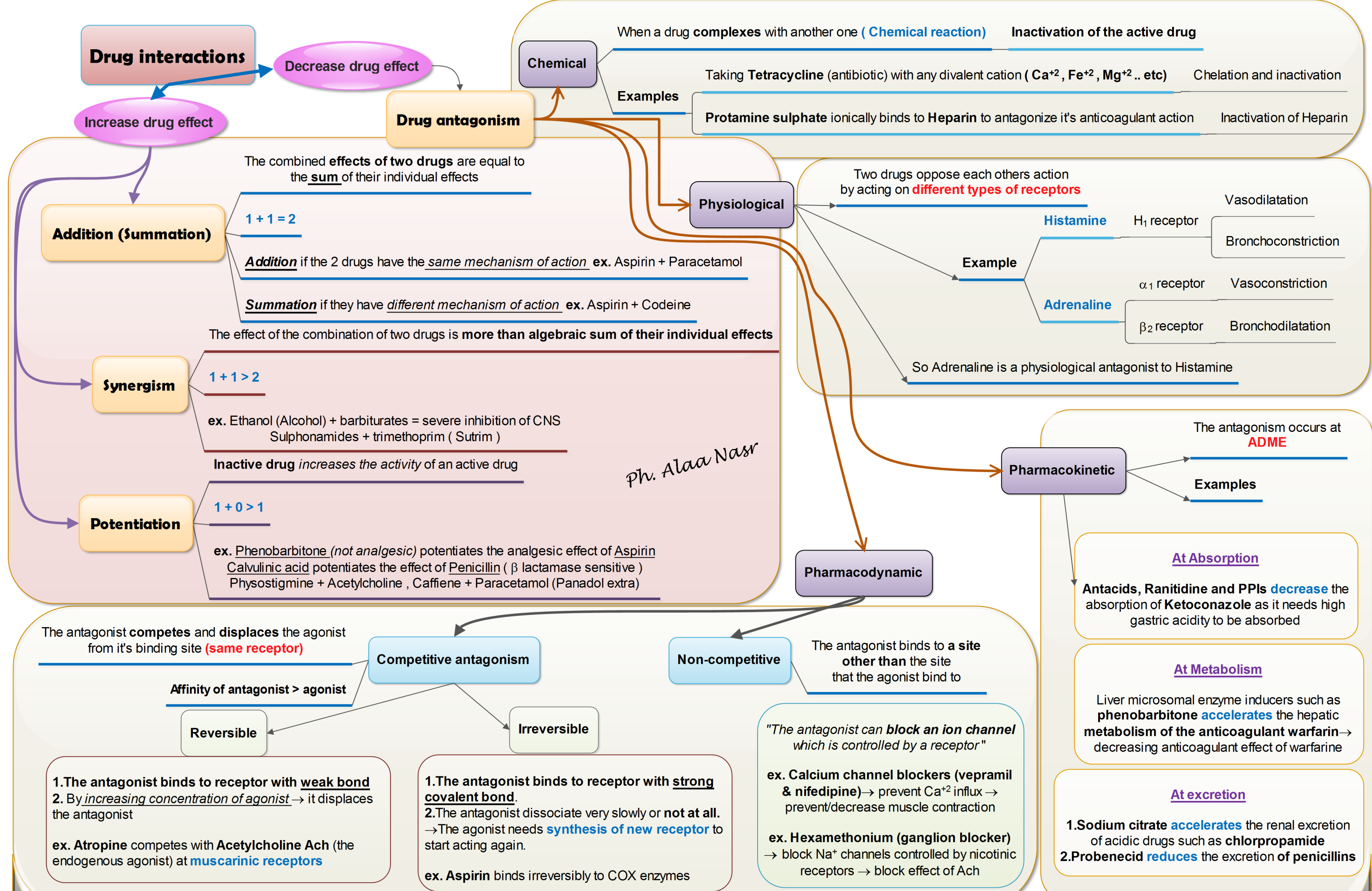
GABA_A receptors

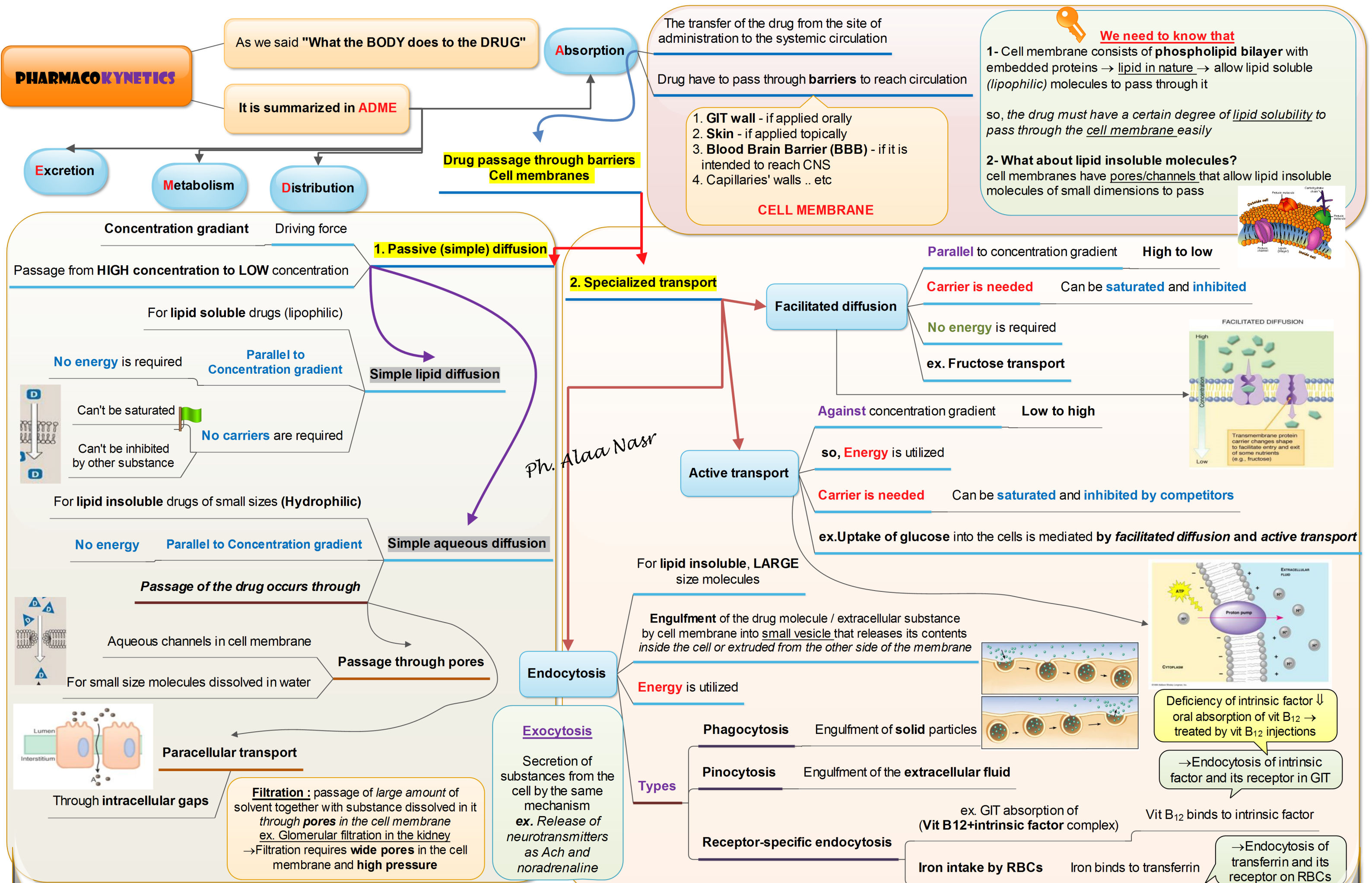
-When GABA binds to it's receptor
-The **Cl⁻** channels open leading to influx of the **Cl⁻** ions
-Leading to **hyperpolarization** of the cell membrane

Nicotinic receptors

-When Ach binds to it's receptor
-The **Na⁺** channels open leading to influx of **Na⁺** ions
-So **depolarization** of the cell membrane occurs







Factors affecting passive diffusion

1. PH of the medium and polarity of drugs

Present as **ionized and unionized** forms

Most drugs are **weak electrolytes**

✓ **Unionized**

To cross the cell membrane the drug must be **more lipid soluble**

Remember

ionized form = have a + or - charge = water soluble
unionized form = NO charge = lipid soluble

Handerson-Hasselbalch equation

This is controlled by

$$PKa = PH + \log \left(\frac{\text{protonated form}}{\text{unprotonated form}} \right)$$

2. Available surface area

Stomach is not the major site of absorption (EVEN ACIDIC DRUGS) !!! WHY!

Surface area of stomach is **small**

Gastric epithelium is lined with **thick mucous layer**

Intestine is the major site for absorption of acidic and basic drugs WHY!

Surface area of the intestine is **large** (1000 times more than the stomach)

Intestinal epithelium is **NOT** lined by thick mucous layer

3. Blood flow

Blood flow to the intestine > Blood flow to the stomach

So, Absorption from intestine is > absorption from stomach

4. Binding of the drug to plasma proteins

Cell membrane is permeable to the drug in the free form

When the drug is strongly bound to plasma proteins

Absorption increase

The drug passes from GIT to plasma → attach to plasma proteins → No return → increase absorption

Remember

PH + POH = 14
PKa + PKb = 14

PKa is the PH at which ionized form = unionized form

For weak acids

ex. Salicylates and Barbiturates

$$PKa = PH + \log \left(\frac{\text{Unionized}}{\text{ionized}} \right)$$



Let's use our brains

In the acidic medium of stomach (PH 1.4)

→ "There would be excess H⁺" see the reaction
→ So, the reaction is **shifted to the left**
→ ↑ **unionized form**
→ **"More lipid soluble"**
→ **absorbed from the stomach to the plasma**

In the more alkaline medium of plasma (PH 6.4)

→ the reaction is shifted to the right
→ ↑ **ionized form**
→ **"More lipid insoluble"**
→ **Trapped in the plasma and don't return back to stomach**

For weak bases

ex. ephedrine, morphine, strychnine

$$PKa = PH + \log \left(\frac{\text{ionized}}{\text{unionized}} \right)$$



Let's use our brains

In the acidic medium of stomach (PH 1.4)

→ "There would be excess H⁺" see the reaction
→ So, the reaction is **shifted to the left**
→ ↑ **ionized form**
→ **"More lipid insoluble"**
→ **NOT absorbed from the stomach**

When the drug reaches the alkaline medium of the intestine (PH 7-8)

→ the reaction is shifted to the right
→ ↑ **unionized form**
→ **"More lipid soluble"**
→ **absorbed from intestine**

For Strong bases

ex. d-tubocurarine

Strong bases have **high PKa** (ex. 10)

So, the drug presents in **ionized form**

NOT absorbed from the whole GIT

So, NOT given orally

Passive flux / diffusion according to concentration gradient is governed by

Fick's law of diffusion

$$\text{Flux} = \frac{\text{Concentration gradient (C}_1 - \text{C}_2) \times \text{Area} \times \text{Permeability coefficient}}{\text{Thickness}}$$

So, Flux (amount of the drug that passes through the cell membrane)

Permeability coefficient

Measures the **mobility** of the drug

Depends on **lipid solubility** "Partition coefficient"

So, ↑ lipid solubility (lipophilicity) → ↑ permeability coefficient → ↑ passage of the drug

Directly proportional to

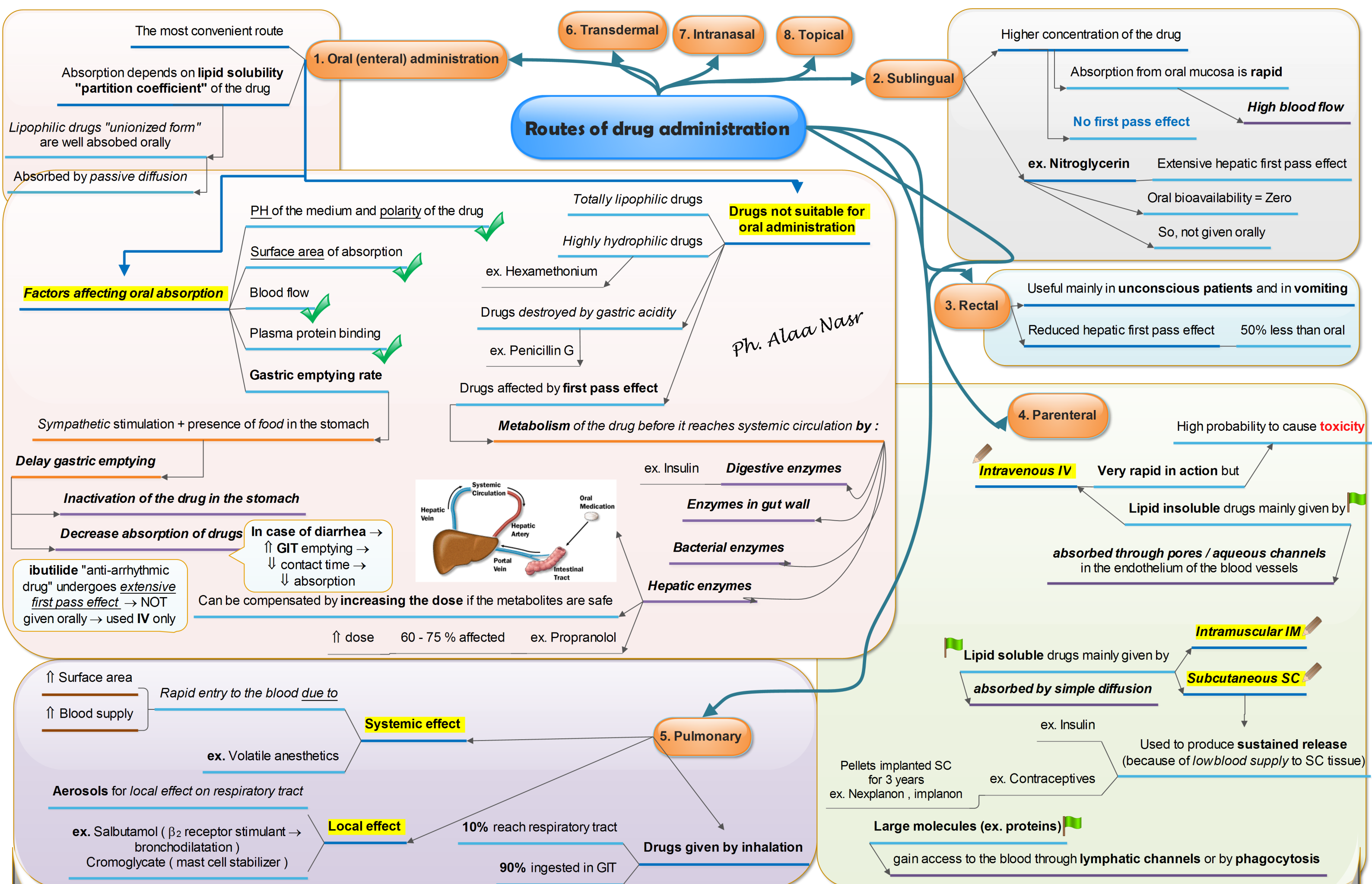
Concentration gradient

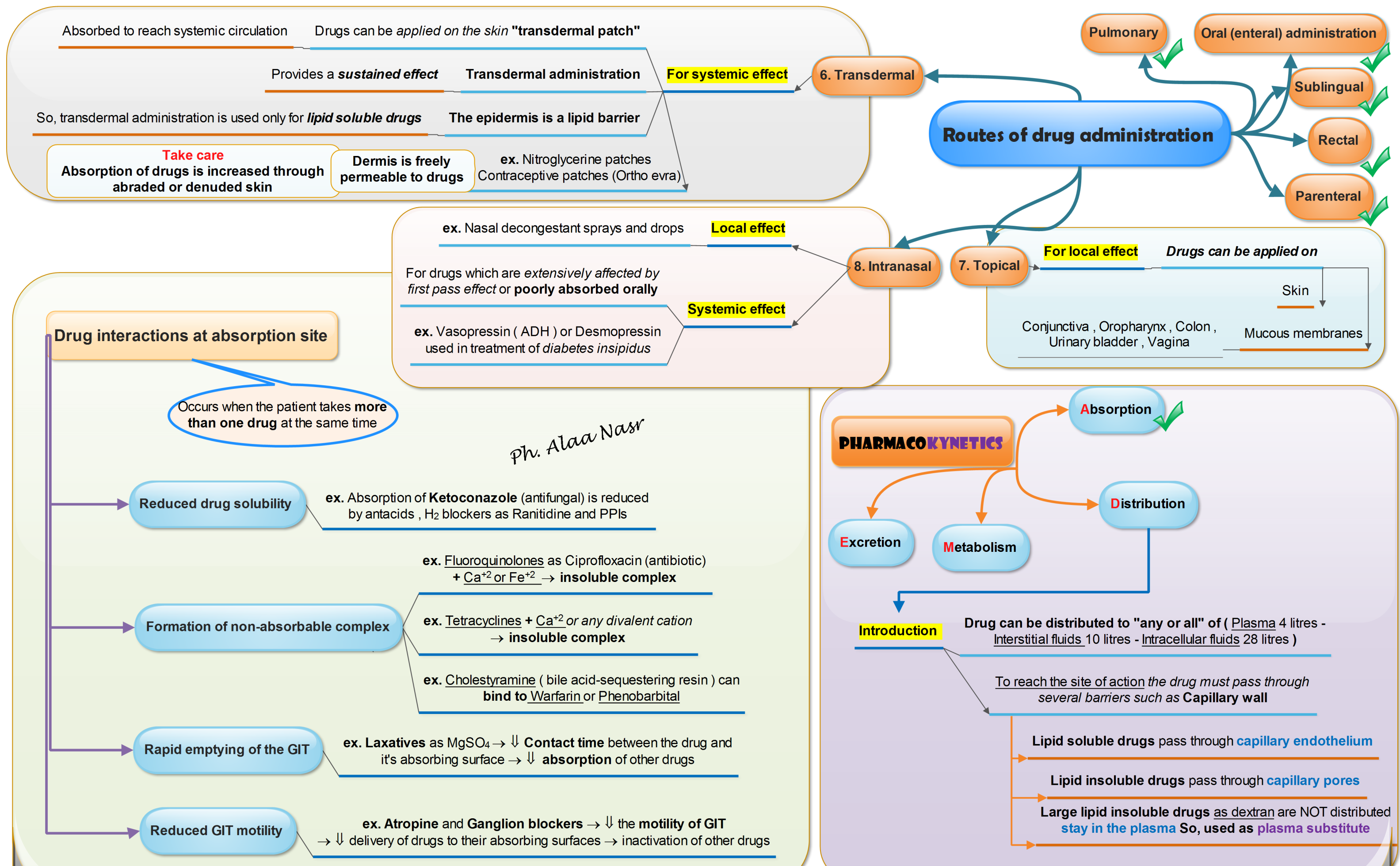
Surface area of cell membrane

Inversely proportional to

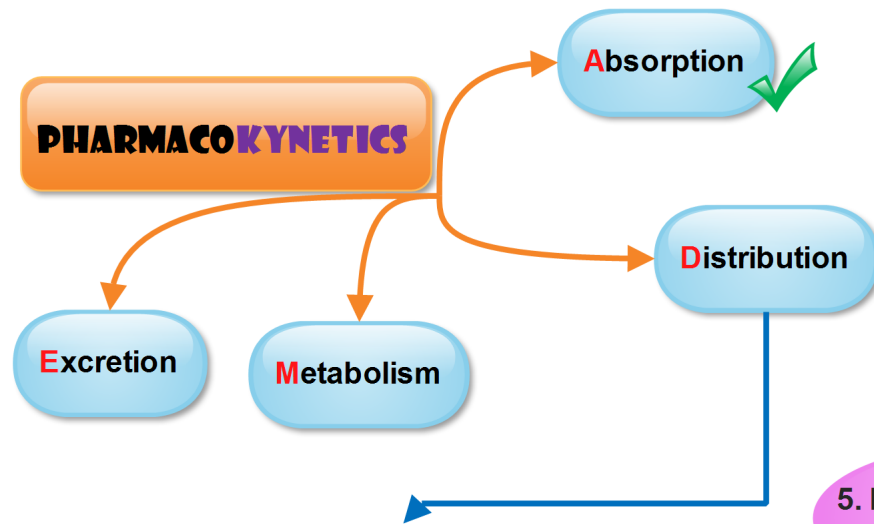
Thickness of cell membrane

Permeability coefficient

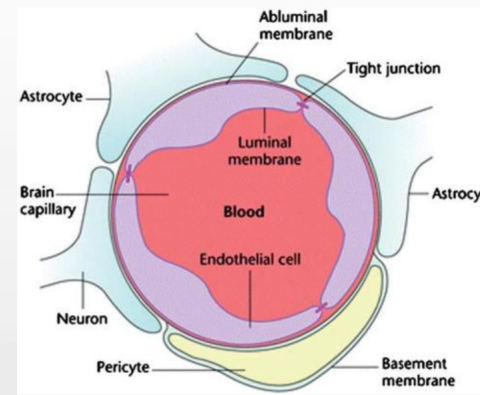




PHARMACOKINETICS



Introduction



Take care

- There is **NO** aqueous diffusion (**no paracellular transport**) across BBB → **ONLY lipid diffusion**
- Amino acids gain access to the brain through **carrier**

So, BBB is only permeable to **lipid soluble compounds**
ex. General anesthetics

But not permeable to **hydrophilic substances**

Glial cells

- Non-neuronal cells that surround neurons
- Hold neurons in place and supply nutrients and oxygen

BBB is a **membrane** that **encapsulates** and **protect** CNS

Capillaries of CNS are enveloped by **glial cells** (*astrocytes*)

Endothelial cells of capillaries and glial cells are connected together by **tight junctions**

BBB does not contain pores

Factors contributing to unequal distribution of drugs

5. Blood brain barrier BBB

Are **high Mwt proteins** present in plasma as **albumin** and **globulin**

Some drugs tend to bind to plasma proteins (become inactive) and are dissociated after a while from them to be active

Some drugs are strongly bound to plasma proteins
ex. **Phenyl butazone** - **Coumarin**

Other drugs occur mainly in free state. ex. **antipyrine**

1. Binding to plasma proteins

Consequences of drug binding to plasma proteins

Concentration of the drug in the blood > in tissues

Protein bound drug acts as **depot / reservoir** → when free drug ↓ → bound drug dissociates from plasma proteins to become free → Active

Increase half life of drug (Not metabolized nor excreted)

In case of **toxicity** or **hypersensitivity** manifestations will take long time to disappear

- In case of hypoalbuminemia (albumin deficiency) → ↑ **free drug** → toxic manifestations may appear
- When two highly protein bound drugs are given together → ↑ **free drug for both** → ↑ therapeutic effect, toxicity and duration of action of both

Take care

- Cell membrane is **only permeable** to drugs in the free form
- **Free drug** has pharmacological actions and can be metabolized and excreted
- **Protein bound drug** is NOT active, NOT metabolized, NOT excreted

Drug interactions at protein binding sites

Drugs with **high affinity** for binding to plasma proteins **displace** drugs with **lower affinity**

ex. **Simvastatin**, **Clofibrate**, **Phenylbutazone** → displace **Coumarin** (anticoagulant) → ↑ free coumarin → bleeding

ex. **Salicylates** → displace **Tolbutamide** (hypoglycemic) → ↑ free tolbutamide → hypoglycemic shock

4. Concentration in body fat

Storage in body fats occurs with **highly lipid soluble** drugs

ex. **Thiopental**, **estrogen**

2. Blood flow

As the blood flow is ↑ to certain organ → it receives ↑ amount of drug

Highly perfused organs
ex. **Brain**, **Kidney**, **Liver**

Receive **high** amount of drugs

Poorly perfused organs
ex. **Fat**, **Tendons**, **Nails**

Receive **low** amount of drugs

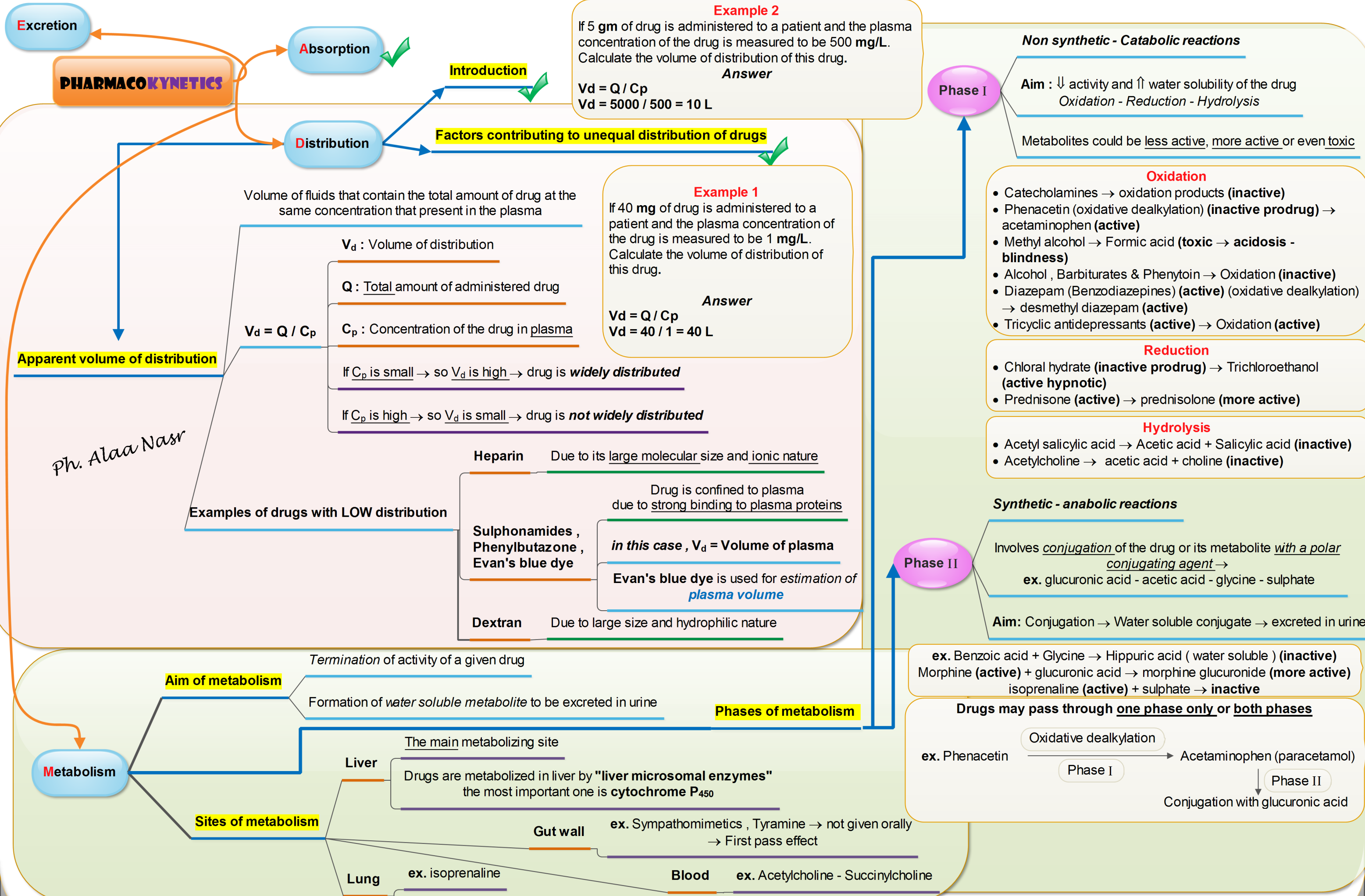
3. Cellular binding (Preferential accumulation)

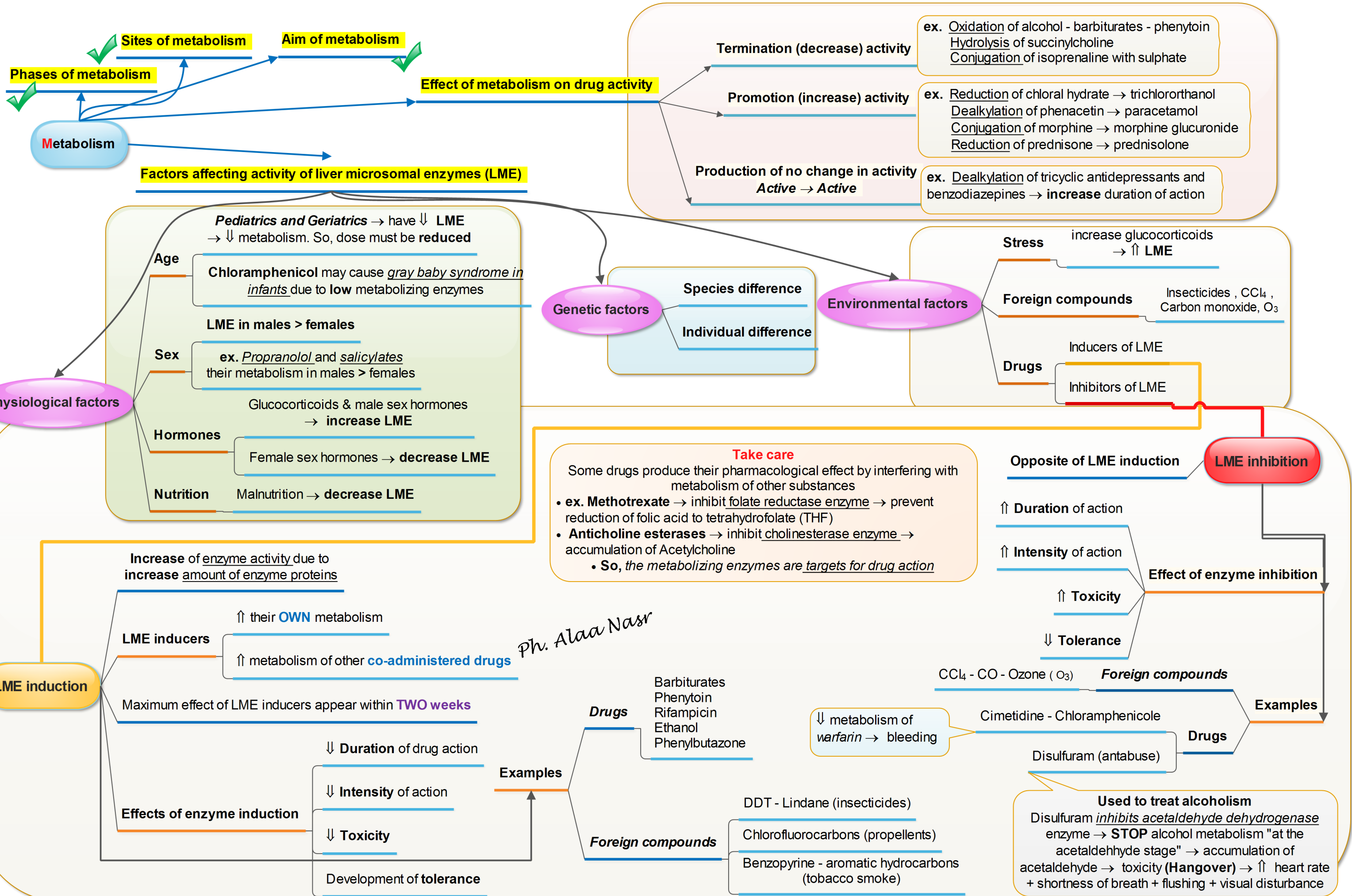
Some drugs have **affinity** for particular constituent of tissues

So, the drug preferentially accumulate in these tissues

ex. **Chlorpromazine** accumulated in → **Brain**
Tetracyclines and **metals** → **Bone & Teeth**
Iodine → **Thyroid gland** (Specialized transport)
Digoxine → **Heart**, **Kidneys**, **Liver**
Arsenic → **Keratin**

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PHARMACOKINETICS

Absorption

Distribution

Excretion

Metabolism

Introduction

Excretion is the second major process by which drug activity is terminated

Elimination of a drug = Metabolism (*biotransformation*) + Excretion

Kidneys are the major site of excretion

Each kidney is composed of 2 parts :
Cortex and medulla

The functional unit of excretion in the kidney is called **nephrons**
each kidney contains about 1 million nephrons

Routes of excretion

Extrarenal route

Lungs, GIT & Bile, Sweat, Saliva, Breast milk

Renal route

3 Steps

1- Glomerular filtration

Blood goes to glomerulus through afferent arteriole →
Filtered under high pressure in **Bowman's capsule "ultrafilter"**
→ Then blood is discharged through efferent arterioles

Only **water** and **small molecules** and ions can pass through Bowman's capsule

Big molecules such as plasma proteins → can not pass
So, **plasma proteins-bound drug can not pass, only free drug can**

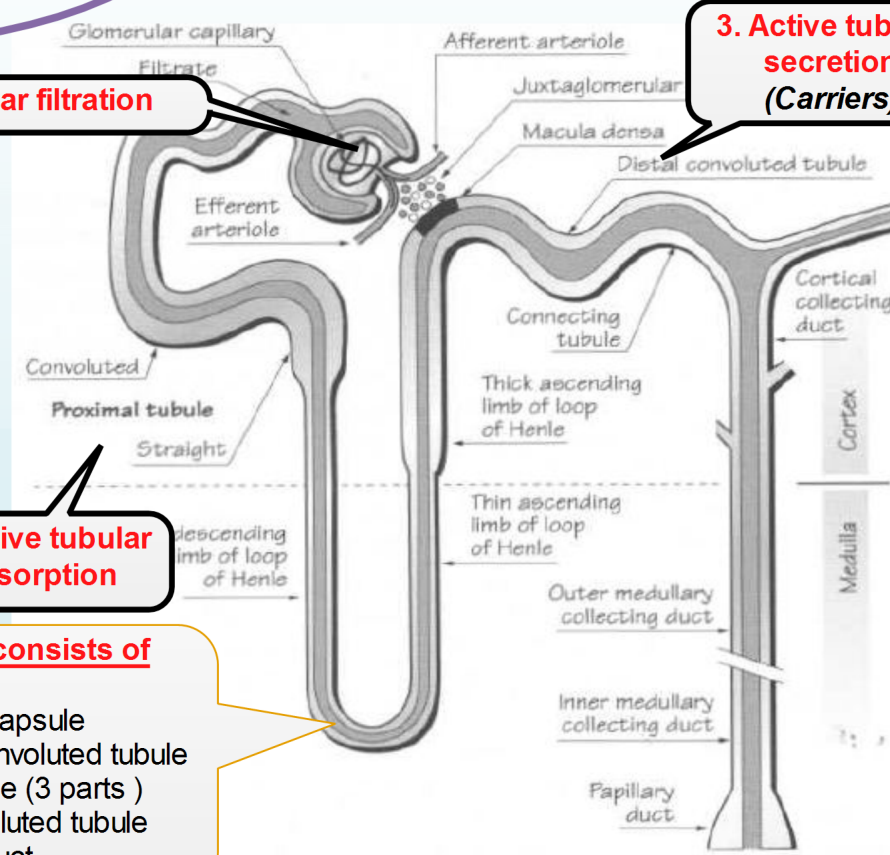
In case of **nephritis** (*inflammation in kidney*) → pores of glomeruli are wider
→ albumin may pass in urine → **albuminuria**

1. Glomerular filtration

2. Passive tubular reabsorption

Nephron consists of

1. Glomerulus
2. Bowman's capsule
3. Proximal convoluted tubule
4. Loop of henle (3 parts)
5. Distal convoluted tubule
6. Collecting duct



3. Active tubular secretion (Carriers)

3- Active tubular secretion

Renal tubules contain transport system (carriers)
used to transfer drugs *against concentration gradient* from **blood** to **tubular fluid**
- using active transport = carriers + energy

Transporters have low specificity

→ Two drugs can compete for the same transporter
→ **decrease** renal excretion of both drugs

2- Passive tubular reabsorption

Passive process, occurs at proximal and distal tubules

Water and other nutrients needed by the body are normally
reabsorbed from renal tubules by **passive diffusion**

So, the concentration gradient of the drug at the end of tubules is **100 times**
more than at the beginning → *due to water reabsorption*

Unionized forms of drug (lipid soluble) → can pass back to blood
→ Passive reabsorption according to concentration gradient

Ionized forms of drug (lipid insoluble) → remain in tubular fluid → excreted in urine

Ionization of drugs depend on PH of urine

Basic drugs are ionized in acidic urine → more excreted

Acidic drugs are ionized in alkaline urine → more excreted

Forced diuresis (ion trapping)

It is the enhancement of excretion of a certain drug
by controlling PH of urine

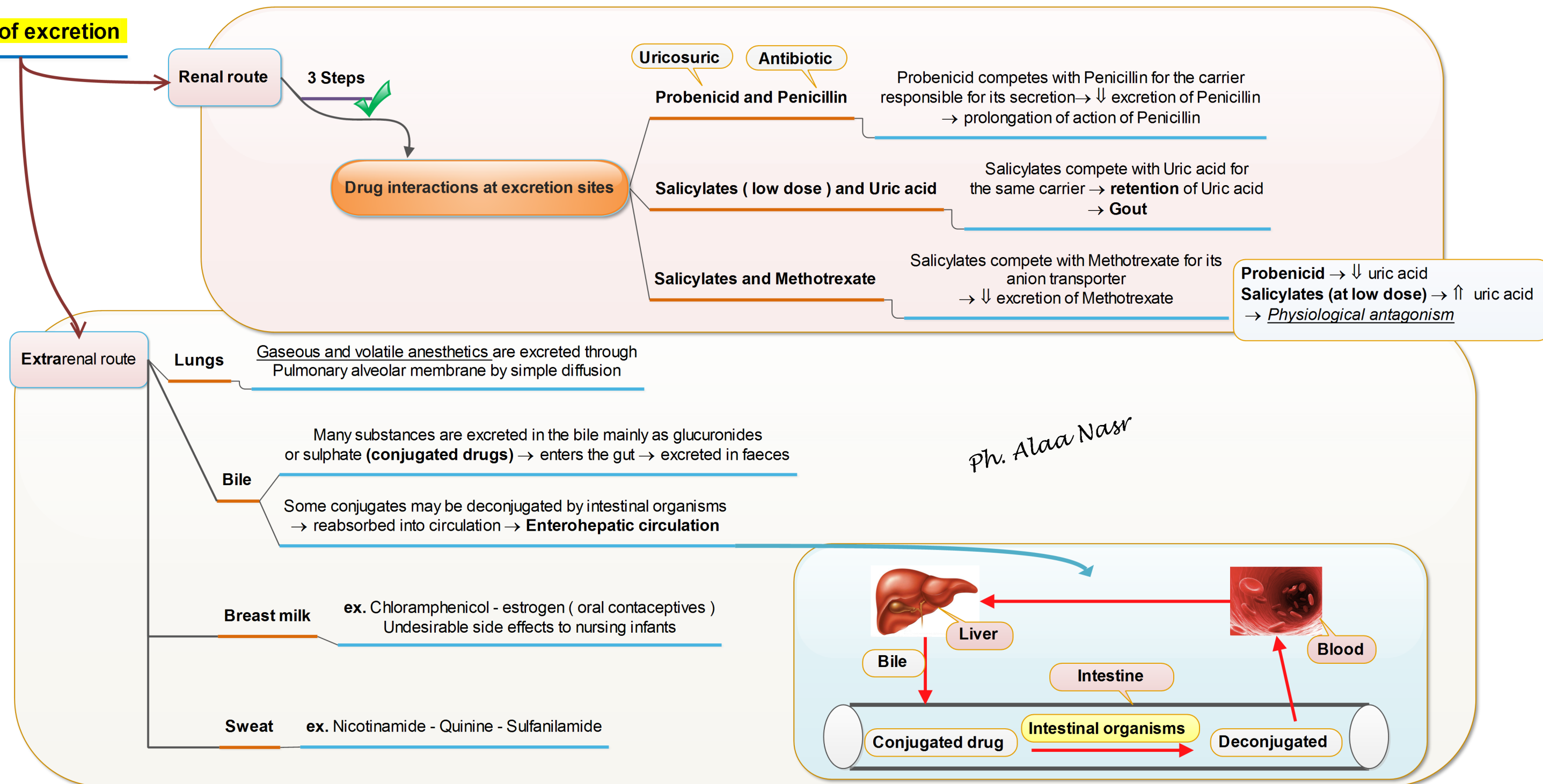
Forced alkaline diuresis

Used for elimination of weak acidic drugs ex. **barbiturates**
through alkalization of urine using **NaHCO₃** → favours ionization
of acidic drugs → prevent tubular reabsorption → ↑ elimination

Forced acidic diuresis

Used for elimination of weak basic drugs
ex. **amphetamine** , **strychnine** , **morphine**
through acidification of urine using **NH₄Cl** → favours ionization
of basic drugs → prevent tubular reabsorption → ↑ elimination

Routes of excretion



Factors affecting drug dosing

- Age**: Child dose = Adult dose X (age in years / age+12) , *If age > 2 years*
- Weight**: Child dose = Adult dose X (weight in pounds / 150) , *if age < 2 years*
- Sex**: Sometimes females are more susceptible to drugs than males
- Pathological status**: Liver or kidney diseases could decrease metabolism & / or excretion of the drug
- Drug combination**: Summation or Addition , Synergism , Potentiation , Antagonism → **Already studied**

Adverse drug reactions

Side effects

These are not the main effect (unwanted) but some times are considered as a clinical use of the drug

ex. Atropine

- **Main effect** → smooth muscle relaxant (anti-spasmodic)
- **Side effect** → dryness of respiratory tract secretions and dry mouth

→ So, may be used during anesthesia to decrease respiratory tract secretions

- **Side effect** → decrease GIT motility constipation

ex. Sildenafil (Viagra®)

- Clinical trials were to use it for treatment of hypertension → but it was found that it has a useful side effect in treatment of erectile dysfunction in men → so, finally it is formulated as a drug for erectile dysfunction



1- Idiosyncrasy / pharmacogenetic factors

Abnormal reaction to a drug due to genetic factors

1 - Succinylcholine apnea → Pseudocholinesterase deficiency

Pseudocholinesterase is an enzyme responsible for degradation of Ach and similar substances mainly in blood

Succinylcholine (similar to Ach) is a skeletal muscle relaxant used before anesthesia by dripping method (drop by drop) and is degraded in blood

In case of deficiency of the enzyme → succinylcholine is accumulated ↑ → causing respiratory failure

Succinylcholine apnea انقطاع في النفس

2- Malignant hyperthermia

Inherited muscle disorder → abnormal increase in Ca^{+2} release from endoplasmic reticulum

Exposure to general anesthetics (ex. isoflurane) and/or succinylcholine → fever, muscle rigidity, tachycardia, lactic acidosis

3- Hereditary methemoglobinemia

Deficiency of methemoglobin (MetHb) reductase enzyme which is responsible for the reduction of Fe^{+3} in RBC's hemoglobin to Fe^{+2} to be able to carry oxygen to tissues → Upon administration of oxidant drugs (ex. Nitrates) → ↑ MetHb → hypoxia and cyanosis

4- Acetylator phenotype

- Slow acetylators (50% of Caucasians)
- Rapid acetylators (90% of Asians)

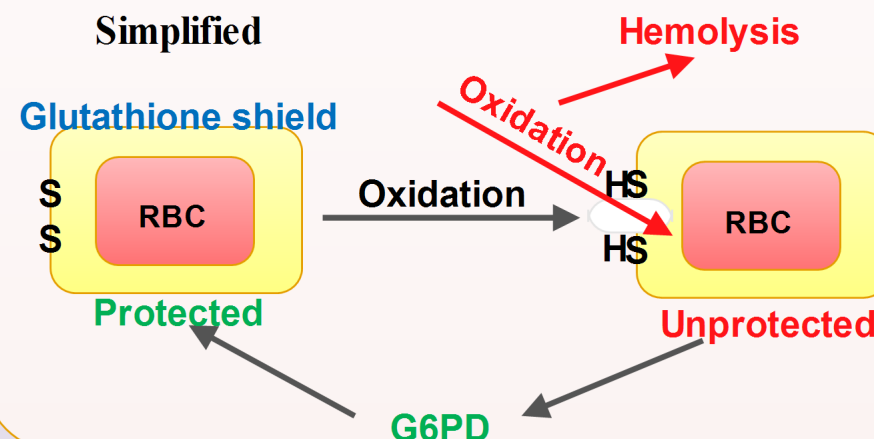
ex. Isoniazide is metabolized by acetylation →

so Slow acetylators → isoniazid toxicity

1. Peripheral neuropathy (isoniazid complexes with vit B₆ → ↓ vit B₆)
2. Bladder cancer
3. Autoimmune disorders

5- Glucose-6-phosphate dehydrogenase deficiency "Favism" أنيميا الفول

G6PD enzyme is responsible for maintaining glutathione (molecules shielding RBCs) in reduced form → prevent hemolysis of RBCs
In case of enzyme deficiency, upon exposure to oxidants (ex. Nitrates, chloroquine, fava beans) → that will oxidize (remove) glutathione shield → exposing RBCs to oxidants and hemolysis



Undesirable effects

These are effects that are totally unwanted (undesired)

2-Tolerance

1. Congenital tolerance

- **Racial tolerance** : Ephedrine does not produce mydriasis in Mongols
- **Species tolerance** : Histamine does not affect rabbit's intestine
- **Individual tolerance** : due to genetic variation

2. Acquired tolerance

It is decreased response to the agonist after its repeated injection in small doses

Drug dose must be increased to maintain a certain pharmacological effect
Occurs over a long period

Mechanisms of Hyporeactivity Drug desensitization

1- **Change in the receptor**: Conformational change in the receptor → normal binding of agonist without opening of ion channels

2- **Down regulation (loss of receptors)**: Prolonged exposure to **agonist** → gradual decrease in number of receptors (receptors are taken into the cell by endocytosis)

3- **Exhaustion of mediators**: ex. Depletion of catecholamines by amphetamine

4- **Liver microsomal enzyme induction**: increase metabolic degradation ex. barbiturates

3-Tachyphylaxis

Acute acquired tolerance → it is a type of tolerance that occurs very rapidly

- Barium chloride in rabbit's intestine
- Using nasal decongestants → causes exhaustion of mediators → so lose their effects upon use for more than nearly 5 days continuously → so, advise the patient not to use the nasal decongestant for more than 4-5 days (stop it and then return after a while)



Tolerance - Tachyphylaxis - Desensitization → are called Hyporeactivity syndromes → effect ↓ upon time

Adverse drug reactions

Undesirable effects

4-Hyper-reactivity syndrome

1- Upregulation (Hyper susceptibility)

Prolonged exposure to **antagonist** or **decreased** concentration of **agonist** → **Upregulation** → ↑ number on receptors

So, Sudden withdrawal of antagonist → agonist will act on **LARGE** number of receptors → **exaggerated response**

ex. Sudden withdrawal of **Propranolol** (β blocker) → Severe tachycardia

→ so, advise the patient **NOT** to quit using it suddenly
It should be stopped within **7-14 days**



2- Accumulation :

Drug effect can increase also when rate of administration > rate of metabolism or excretion

5-Drug dependence

1- Habituation

- It is **emotional** or psychological dependence (**psychic craving**) for a drug
- If the drug is **stopped** → the individual might suffer from some **emotional distress** for a short period of time but finally will **recover**

ex. Coffee , Tea , Tobacco smoking

2- Addiction

- It is **psychic craving** and **physical dependence** on a drug
- Through repeated administration of the drug → body tissues become accustomed to it → to the extent that they require the drug to function normally !
- If the drug is **stopped** → severe withdrawal symptoms / abstinence syndrome

ex. Morphine , Alcohol , Barbiturates

6- iatrogenic effect

It is drug induced complication (the drug itself produces a disease)

Examples

- **Chlorpromazine** (antipsychotic) used to treat schizophrenia
- **During treatment** symptoms of parkinsonism develop !!

7-Teratogenic effect

These are **fetal malformations** produced by certain drugs **when used during pregnancy**

Examples

- **Isotretinoin** a drug used for the treatment of acne حب الشباب
- **Should be stopped before getting pregnant** by at least **6 months** !



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